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Limb-Saving Surgery, Survival, and Prognostic Factors for Osteosarcoma: The Hungarian Experience

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Background and Objectives: There are many factors thought to have an influence on the prognosis of osteosarcoma that have been reported in the literature. Their significance, however, still remains controversial in most cases. Experience with osteogenic sarcoma (OS) was reviewed in order to evaluate surgical results and survival and to determine the prognostic factors.

Methods: Ninety-six patients with high-grade osteosarcoma of the extremities were treated between 1986 and 1997 in the authors' institution. They were divided into 3 groups: In group I, all 75 patients with nonmetastatic OS received intensive chemotherapy (high-dose methotrexate, doxorubicin, ifosfamide, and cisplatin) and underwent surgery. In group II, 9 patients already had metastases at the time of referral. In group III, 12 patients received chemotherapy in delayed or suboptimal form.

Results and Conclusions: In group I, there were local recurrences in 3 patients (7%) and metastases in 8 patients (20%) with limb-saving, whereas these numbers were 1 (3%) and 14 (38%) in those who had amputation. The 5-year disease-free survival (DFS) was 72% and 69% in the limb-saving and amputation groups, respectively. In groups II and III, 5-year DFS was extremely poor, 10% and 20% only, underlining the importance of stage and intensity of chemotherapy, respectively. With univariate analysis, sex, duration of symptoms, and radiographic appearance of OS had no prognostic value, whereas tumor volume <60 cm^3, wide or radical surgical margin, distal location of OS, cartilagineous ground substance <20%, and response to chemotherapy were positive prognostic factors. The last 4 variables maintained their significance in the multivariate Cox model as well. Age >30 years showed indirect negative influence on the final outcome through enhanced intolerability to the drugs and less cooperability of the patients. The results on survival with limb-saving surgery were well comparable with those of amputation.

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KEY WORDS: limb-saving; survival; prognostic factors; osteosarcoma

INTRODUCTION

The past 25 years have brought essential changes in respect to the survival outcome of highly malignant central osteogenic sarcomas. In the works of Rosen et al. from 1979 and 1982 [1,2], adjuvant chemotherapy

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supplemented with intensive preoperative neoadjuvant chemotherapy resulted in a 5-year tumor-free survival of 60%–75% in contrast to the 15%–20% observed in the documented control group. Limb-sparing surgery is coming to the forefront, performed in 60%–70% percent of cases. When indicated, limb-sparing surgery provides results comparable with those of surgical resections both in regard to incidence of pulmonary metastases and 5-year disease-free survival (DFS) [3,4,5].

Parallel with the improvement of results, more and more publications deal with the role of prognostic factors [6–11]. The findings, however, are quite often contradictory, the cause most often being a low number of cases, different chemotherapeutic protocols, too short a follow-up, the comparison of patients who are in different stages, and improper statistical analysis. [7].

The present study gives an evaluation of the role of various prognostic factors in view of the treatment results of 96 patients with osteogenic sarcoma.

MATERIALS AND METHODS

From January 1986 to December 1997, 121 patients with highly malignant central osteogenic sarcomas of the extremities were treated at the bone tumor unit of our department. Twenty-five patients were excluded from the evaluation due to the following causes: 14 patients were lost to follow-up or continued treatment at other institutions, 2 patients refused any treatment, and in 5 cases treatment was not offered because of the patient's general condition and the extent of the tumor. Three patients died due to complications arising from the effects of chemotherapy and 1 died from another disease. The 96 patients under study were divided into 3 groups: group I comprised 75 patients receiving chemotherapy according to the strict protocol guidelines (high-dose methotrexate, doxorubicin, cisplatin, ifosfamide). According to the surgical stages of Enneking et al. [12], 15 patients belonged to II/A and 60 patients to II/B. Group II comprised 9 patients in whom pulmonary metastases were present at presentation. In the remaining 12 patients (group III), chemotherapy was delayed and administered in suboptimal or incomplete form due to various causes (intercurrent disease, psychological factors, lack of cooperation, intolerance to chemotherapy).

In total, 21 patients did not receive neoadjuvant chemotherapy prior to surgery, while 55 received both pre- and postoperative adjuvant treatment.

The case history of every patient was known, so the time between appearance of symptoms and establishment of the diagnosis (period of anamnesis) could be determined. Apart from the blood tests, bone isotope tests, chest radiographs, or computed tomography (CT) scans were obtained for tumor stage determination, abdominal ultrasound scans were obtained to exclude metastases involving other organs, and two-directional radiographs, CT scans, or magnetic resonance images (MRI) were obtained to determine the local spread. Follow-up began from the time of establishing diagnosis, based on the histological examination of the exploratory biopsies, and ended with the death of the patient or the last follow-up (March 1999). The mean follow-up period was 62 months (range, 16–158). The average survival period, EFS, and the total 5-year survival periods were calculated.

Tumor size was determined by three-dimensional greatest measurements on two-directional radiographs, CT scans, or MRI scans. Tumor volume was calculated on the basis of an ellipsoid formula, using these measurements: absolute height × absolute width × absolute depth × 0.52 [13].

By radiomorphology, clearly lytic, sclerotic, and mixed tumors are distinguishable.

On the basis of the dominant cell type (semiquantitative evaluation: minimum 60%–80%), histological examination allows for differentiation among osteoblastic, chondroblastic, fibroblastic, telangiectatic, and mixed forms. Based on another grouping [14], differences could be made between cases in which the ratio of metaplastic chondroid tissue in the tumor exceeded 20%.

The effect of preoperative chemotherapy as well as the tumor's degree of histological regression were also studied by means of semiquantitative methods known from the literature [15]. The cases were divided into 3 groups: tumors showing good response to preoperative chemotherapy (tissue necrosis >90%, surviving cells <10%), tumors showing moderate response (surviving tumor cells 10%–50%), and tumors not responding to chemotherapy (surviving tumor cells >50%).

Surgical staging was done according to the method of Enneking et al. [12], with differentiation among highly malignant intracompartmental osteogenic sarcomas (II/A), extracompartmental lesions (II/B), and osteogenic sarcomas with manifestation of metastases present on recognition of the disease (III).

The forms of surgical intervention were limb-saving and amputation (rotation plasty). The staging criteria of Enneking [16] were applied to determine surgical radicality, but due to the low number of cases from the viewpoint of statistical analysis, the 66 radical and wide cases and the 9 marginal and intralesional cases, respectively, were evaluated as joint groups.

Statistical Analysis

Statistics were calculated using the BMDP Statistical Software pack [17]. The Kaplan-Meier survival curve [18], the Fischer's exact test, the *t* test, and the Mann-Whitney probe were used for the univariate survival analyses. The Cox-Mantel test was used to show the significance between the curves of the Kaplan-Meier survival tables. The multivariate analyses of the prognostic

factors were done using the proportional regression hazard model of Cox [19].

RESULTS

Group I

Group I consisted of 75 patients suffering from highly malignant nonmetastatic central osteogenic sarcoma. This group comprised 35 female and 40 male patients with a mean age of 17.4 years (range, 8–53). The locations of lesions were as follows: distal femur, 30; proximal humerus, 10; distal tibia, 6; distal humerus, 2; calcaneus, proximal fibula, and distal radius, 1 each. It was only in 15 cases (20%) that the tumor did not break through the cortical bone and remained intracompartmental (stage II/A); the other 60 cases (80%) were extracompartmental (stage II/B).

Surgical results. Limb-saving surgery was performed in 39 patients (52%), while amputation was done in 36 cases (48%). Median survival related to the 75 patients was 65 months, with 5-year survival being 73% and 5-year EFS being 72%. These data were noted to be 73% and 72%, respectively, in those who had limb-saving surgery and 71% and 71% in the amputation group. Following limb-saving surgery, local recurrences were detected in 3 (7%) of the 39 cases, with only a single occurrence following amputation (2%). Pulmonary metastases developed in 8 of the patients receiving limb-saving surgery (20%) and in 14 who had amputation (39%). Seven of these patients did not live to 5 years following surgery.

Sixty-six of the patients (88%) received radical surgery or resection was done with wide margins, while 9 (12%) were marginal and intralesional. In the latter cases, there were 4 events of local recurrences (following 1 amputation and 3 limb-saving surgeries). The patients receiving radical surgery had a 5-year survival of 80%, while 5-year survival for the marginal or intralesional cases was only 44%.

Univariate statistical analysis showed no significant differences between the survival of patients who underwent limb-saving surgery or amputation (Fig. 1, $P = 0.67$). More notable, although not significant, was the deviation observed regarding the survival of the stage II/A and II/B patients ($P = 0.30$). Significant differences in survival rate, however, were found between the groups treated by radical or wide margins and marginal or intralesional margins (Fig. 2, $P = 0.017$), which remained a prognostic variable in the multivariate regression model, too (Table I).

Duration of symptoms. The duration of symptoms prior to presentation of the patients ranged from 0–12 months (average, 3.3 months). Duration of the symptoms had no effect on EFS.

Age. The mean age of the 75 patients was 17.4 years. The patients were divided into 3 groups according to age.

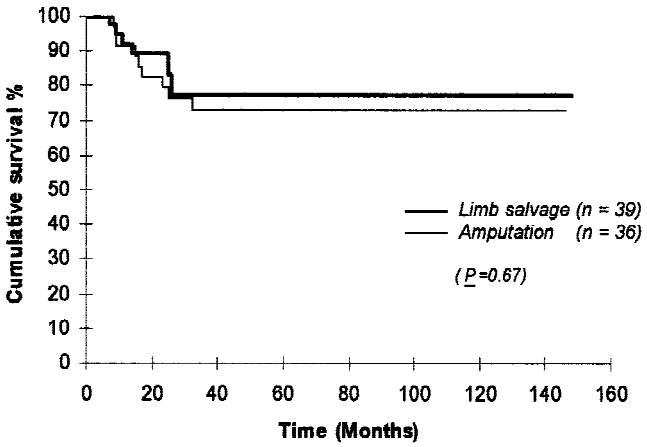

Fig. 1. Disease-free survival for patients who underwent limb salvage vs. amputation procedures.

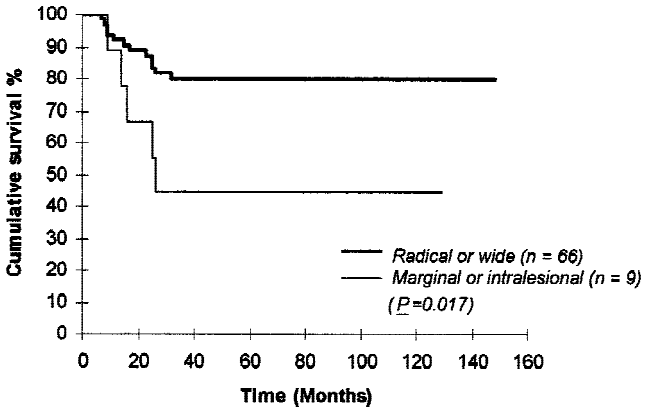

Fig. 2. Disease-free survival for patients who were treated by means of radical/wide vs. marginal/intralesional surgical margins.

The first group comprised 21 (0–13 years), the second 47 (14–29 years), and the third 7 patients (≥30 years). Relationship between age and survival was studied. In all 3 groups, limb-saving surgery and amputation were performed in approximately identical proportions, and the patients received intensive chemotherapy. No significant differences were found in survival among the 3 groups according to age (Fig. 3, $P = 0.75$), that is, if the patients >30 underwent complete chemotherapy according to protocol, their life expectancy was the same as for the younger groups.

Sex. Group I comprised 40 male and 35 female patients. Studies were carried out in relation to the role of sex, if any, in survival. According to the univariate statistical analysis [18], the life expectancy for female patients proved to be somewhat better than for males, but the difference was not significant ($P = 0.15$).

Radiographic appearance. On the basis of traditional radiographs, the central osteogenic sarcomas were thought to be sclerotic in 14 cases, clearly lytic in 18, and

TABLE I. Proportional Hazard Model for Significant Survival Factors in Osteosarcoma Without Histological Response as Variable (n = 75)

Variables	Regression coefficient	Standard error (SE)	Coefficient/SE	P
Chondroid tissue content	1.3690	0.4948	2.7670	0.0080
Site	−0.7319	0.3558	−2.0572	0.0371
Surgical margins	0.9496	0.4908	1.9348	0.0331

Global χ^2: $P = 0.0007$.

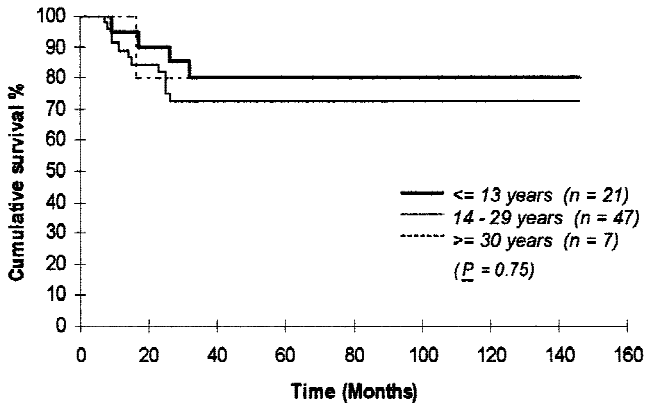

Fig. 3. Disease-free survival for patients aged ≤13 years, 14–29 years, and ≥30 years.

of mixed appearance in 43. The radiographic appearance of the tumors and survival showed no statistical relationship at all.

Site. In respect to their location, the osteogenic sarcomas were grouped in 3. The proximal part of the humerus and femur were regarded to be of proximal location (14 cases), the lesions developing in the distal femur and in the proximal part of the tibia and the fibula were regarded as being distal *a* group (51 cases), while the osteogenic sarcomas developing in the distal radius, tibia, distal fibula, and tarsal bones were considered as distal *b* group (10 cases). The proximal and distal *a* groups were found to have a basically equivalent survival, while the distal *b* group showed an essentially better survival (Fig. 4, $P = 0.03$). The first 2 had a 5-year survival of 62% and 63%, respectively, while the figure for the distal *b* group was 92%. Site was also a significant predictor for EFS in multivariate analysis (Tables I and II).

Size. By use of different cutoff points, comparisons were made between the relationship of survival and tumors with different volumes. Patients with a tumor volume ≤60 cm^3 had a significantly better prognosis ($P =$ 0,061) and are all still alive (Fig. 5). The increase in tumor volume had an adverse effect on the survival of the patients; there were, however, no significant differences among the various groups. The size of the tumor, however, lost its significance as a prognostic variable in the multivariate analysis.

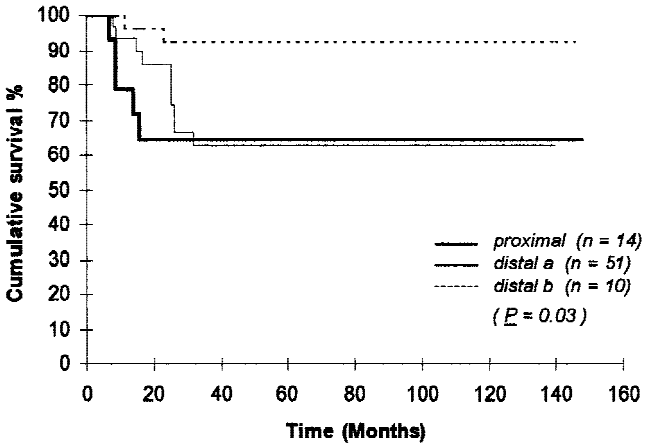

Fig. 4. Disease-free survival by location of the tumor. See text for explanation of categories.

TABLE II. Proportional Hazard Model for Significant Survival Factors in Osteosarcoma With Histological Response as Variable (n = 46)

Variables	Regression coefficient	Standard error (SE)	Coefficient/SE	P
Histological response	−2.0105	0.6462	−3.1111	0.0002
Site	−1.6278	0.6088	−2.6738	0.0032
Chondroid tissue content	1.6251	0.6903	2.3542	0.0222

Global χ^2: $P = 0.0016$.

Histological subgroups. According to dominant cell types, distinction could be made between osteoblastic (42 cases), chondroblastic (8 cases), fibroblastic (6 cases), telangiectatic (6 cases), small cell (3 cases), and mixed cell (10 cases) forms. In case of the latter, no unambiguous dominant cell type could be determined. With the exception of the osteoblastic subgroup, the rest were too few in number to be able to perform statistical analysis; therefore, these were all combined and then 2 groups formed: osteoblastic (42 cases) and all the rest (33 cases). There were no significant differences between the 2 groups according to survival. Other grouping, however, showed notable differences in survival when using the method of Delling et al. [14] based on the chondroid tissue content of the tumor. In 59 cases where the chondroid tissue amount was <20%, the 5-year survival was >80%, while in 16 cases with ≥20% chondroid tissue, it was only 50% ($P = 0.006$). The amount of chondroid matrix kept its significance in the multivariate analysis (Tables I and II).

Neoadjuvant chemotherapy. Of the 75 patients, 54 received both pre- (neoadjuvant) and postoperative (ad-

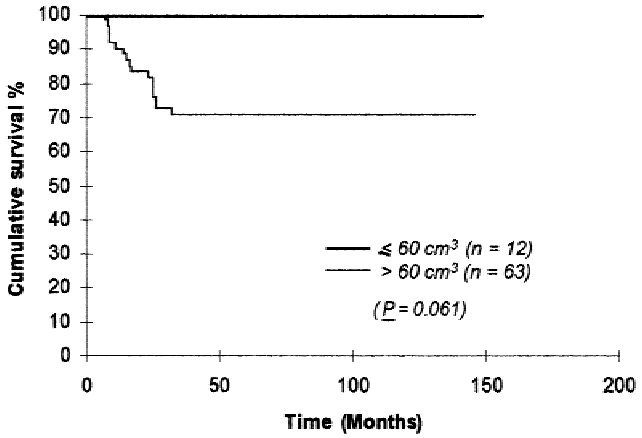

Fig. 5. Disease-free survival depicted by the volume of the tumor ≤ 60 cm^3 vs. >60 cm^3.

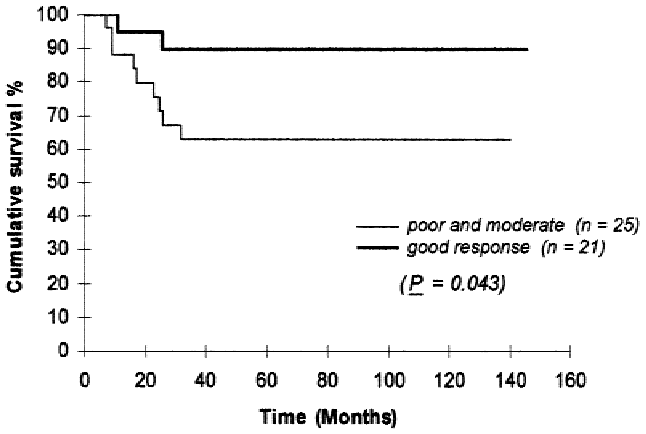

Fig. 6. Disease-free survival by histologic response to preoperative chemotherapy: poor and moderate response vs. good response.

juvant) chemotherapy, and 21 patients received only postoperative treatment. The majority of the latter patients already had osteogenic sarcoma infiltrating the visceral and neural components upon presentation; therefore, immediate amputation was performed. With respect to survival, a considerable difference ($P = 0.02$) was noted in favor of the patients receiving preoperative chemotherapeutic treatment. In their cases, the 5-year survival was 81%, in contrast to the 58% observed for those who received only postoperative chemotherapy.

Histological response to chemotherapy. Data from 46 patients were accessible for studies of the effect of preoperative chemotherapy and the determination of tumor necrosis. Of these, 21 patients (46%) responded well (tumor necrosis >90%), 11 (24%) showed moderate response (tumor necrosis 50%–90%), and 14 (30%) responded poorly (tumor necrosis 0%–50%). Survival showed moderate but significant differences when the Kaplan-Meier curve was made up of 2 groups: those responding well and the combination of those who demonstrated moderate and poor responses (Fig. 6, $P = 0.043$). On the contrary, upon studying the 3 groups separately, the groups exhibiting good and moderate responses seemed to show similar behavior in relation to survival, while the group of poor responders showed a highly significant ($P = 0.001$) degree of worse survival.

Multivariate statistical analysis. All the variables described in Materials and Methods were studied in a complex manner using multivariate statistical analysis (Cox hazard model). Since the histologic response to preoperative chemotherapy could be studied in only 46 of the 75 patients of group I, the multivariate analysis was done in 2 forms: one for the 46 patients with tumor necrosis due to chemotherapy (Table II) and the other comprising all 75 patients, without consideration of chemotherapeutic sensitivity as a variable (Table I). In the first form, using the Cox hazard model, the histologic response to chemotherapy proved to be the most significant factor, having considerable influence on survival. This was followed in decreasing order by tumor location and chondroid tissue content (Table II). When tumor necrosis as a variable was excluded, the factors influencing survival in the 75 patients were found to be, in decreasing order, chondroid content of the tumors, their location, and the radicality of surgery (Table I). The validity of regression was tested using the global χ^2 test and was found to be $P = 0.0016$ for Table II and $P = 0.0007$ for Table I. The Cox regression method evidenced a rather noteworthy relationship between the aforementioned variables and survival in both models.

Group II

The 9 osteogenic sarcoma patients already showing metastases upon presentation received intensive adjuvant chemotherapy, similar to the patients of group I. Their mean age was 26.1 years. As primary surgical intervention, amputation was performed in 6 cases and limb-saving in 3 cases, then 3 cases underwent pulmonary metastatectomy. The mean survival period of all patients was 30 months; 3 patients are still living with persisting pulmonary metastases (3 years, 2 years, and 1 year after recognition of the tumor). Only a 72-year-old woman with persisting pulmonary metastases had a 9-year survival period following recognition of her osteogenic sarcoma.

Group III

A total of 12 patients did not receive chemotherapy in an adequate magnitude and/or at time intervals being in accordance with the protocol. Among the causes were the psychological state of the patients, their inability to cooperate properly, and oversensitivity to medication.

In contrast to the mean age in group I (17.4 years), the mean age in group III was 28.6 years. For all 12 patients, the total survival period was on average 18 months. Eight

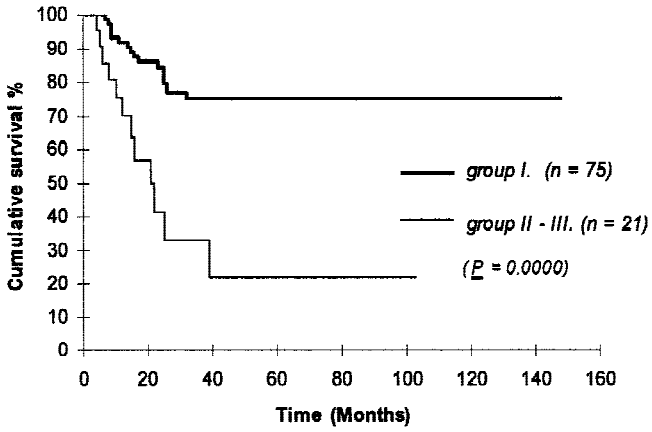

Fig. 7. Disease-free survival for patients in group I (high-dose intensive chemotherapy + surgery in nonmetastatic osteosarcoma) vs. group II (metastatic osteosarcoma) plus group III (suboptimal chemotherapy + surgery).

patients died, while 4 are currently tumor-free survivors (2 years and 1 year following discovery of the disease). Groups II and III displayed survival curves of similar course and were significantly worse than those for group I (Fig. 7, $P = 0.0000$)

DISCUSSION

Group I was particularly suitable for studying prognostic factors. This homogeneous (nonmetastatic) group comprised a statistically estimable case number (75 patients), with each patient having surgery and receiving intensive chemotherapy according to protocol.

In respect to patients who underwent amputation (71%) and those who had limb-sparing surgery (73%), the 5-year EFS of group I conforms with the values of 54%–80% stated in the literature [10,20–22]. Limb-sparing surgery is to be recommended for the patient only if the life expectancy thereby is not worse compared with amputation. Our experiences support the literature data [8,9,23] favoring limb-saving surgery. Consequently, although to a lesser degree, there is a slight but significant increase in the number of local recurrences. In contrast, however, essentially better life quality can be gained in addition to identical 5-year survival (Fig. 1).

In itself, local recurrence is a determinative negative prognostic factor. Survival even after radical removal (amputation) of a recurring tumor is quite poor, about the same as the 10%–20% 5-year survival of metastatic osteogenic sarcoma at the time of diagnosis. Simon et al. [23] reported that 16 of their 17 patients with recurrences died despite radical surgery, while the figures were 23 of 19 patients in the study of Winkler et al. [24]. All 4 of our patients with local recurrences also died due to pulmonary metastases.

The studies of Bacci et al. [25], Glasser et al. [8], Springfield et al. [26], and Winkler et al. [27] in relation to surgical margins call attention to the close correlation between surgical radicality and local recurrences and 5-year survival, respectively. In our series, 7 marginal and 2 intralesional surgical interventions were followed by 4 local recurrences, from which all 4 patients died. It is not suprising therefore that both the univariate and multivariate survival analyses gave evidences of considerable differences between the survivals of the wide + radical and marginal + intralesional patient groups ($P = 0.017$).

Taylor et al. [28] and Bentzen et al. [29] found an adverse correlation between the duration of the symptoms and survival changes. Our data could not confirm this finding.

Male sex (Petrilli et al. [10]) and female sex (Glasser et al. [8]) proved to be a negative prognostic factor. In our study, survival of females was somewhat better, though not significantly ($P = 0.15$). In accordance with others, we do not consider sex to be an essential prognostic factor.

Results are also contradictory with regard to the age of the patient as a prognostic factor. No differences were noted by Spanier et al. [30] and Petrilli et al. [10] between the results of various age groups, while others observed worse survival for patients younger than 13 [9] and older than 30 [9,29]. In general, patients >30 are excluded from evaluations, partly because of their few number and partly because of intolerance to chemotherapy. Our results did not exhibit survival differences between the various age groups. Patients >30 years showed chances of survival corresponding to those of the younger group when high-dose intensive chemotherapy was given in accordance with the protocol. In the case of older patients, however, there were frequent occurrences of poor cooperation, intolerance to chemotherapy, and other complications, resulting in chemotherapy being given with considerable delay and not according to protocol. These patients were excluded from the protocol and placed in group III, as a result of which the average age of this group was 28.6 in contrast to the age of 17.4 of group I.

The location of osteogenic sarcoma as a prognostic factor shows divergent estimations in the literature. Axial location (spine, pelvis, ribs) was found to have poor prognosis [29]; proximal humerus location gave better results in the studies of Glasser et al. [8] and Meyers et al. [9], while Provisor et al. [22] and Taylor et al. [28] found the humerus and femur sites to be negative prognostic factors contrary to the proximal tibia location and sites farther from the trunk. In our material, the osteogenic sarcomas located far from the trunk proved to have better prognosis ($P = 0.03$) by the univariate and multivariate analyses. The value of this finding, though, is lessened by our small case number.

Earlier, tumor size was considered a less important

factor than the surgical stage of the tumor [8,29,31], with attention called to the inaccuracy of volume measurements [8]. The two-directional radiograph-based calculations on tumor volume assisted by the ellipsis formula (height × width × depth × 0.52) show good correlation with the CT- or MRI-based computerized volume measurements, according to the studies of the Cooperative Osteosarcoma Study Group (COSS) workgroup [3]. Their results have shown that 4 of 53 patients developed metastases, in whom tumor volume was <150 cm^3, while in others, relapse was manifest in 40%–60%. Our study also exhibited survival rates inversely changing with the increase in tumor volume. Significant differences, however, were only found between the >60 cm^3 and ≤ 60 cm^3 groups.

Several attempts have been made at demonstrating correlation between the histological subgroups and survival. The majority of authors have failed to find any relationship [8,21,26], while Bacci et al. [32] considered the telangiectatic osteogenic sarcoma and Petrilli et al. [10] the osteoblastic form to have better prognosis as compared with other histological subgroups. The latter was manifest in our material as well but with nonsignificant results ($P = 0.32$). The evaluation was presumably influenced by the fact that the vast majority of cases showed mixed histological structure. The COSS workgroup [14] had earlier found close correlation between the chondroid tissue content of osteogenic sarcomas and response to chemotherapy. Later studies, however, failed to confirm chondroid content to be a factor influencing survival. The chondroid tissue content of the osteogenic sarcomas in our material was a strong prognostic factor in both the uni- and multivariate survival analyses (Tables I and II). The osteogenic sarcoma group with tumors >20% chondroid tissue showed considerably worse prognosis ($P = 0.006$).

Several workgroups [8–10,15,22,32] have dealt with the issue of the relationship between tumor necrosis on the effect of preoperative chemotherapy and survival. In both uni- and multivariate statistical analyses, the chemotherapeutic sensitivity of osteogenic sarcomas has been a strong prognostic factor. While cases showing chemotherapeutic sensitivity demonstrate 5-year survival of around 91%–95%, tumors resistant to chemotherapy reveal a mere 50%–65% figure, with the rate of local recurrences also being higher [8,9,22,33]. Our grading, similar to the three-part scale of Picci et al. [34], was developed with practical viewpoints in mind. Here, the group with good response had tissue necrosis of >90%, the moderately well responding formed tumor necrosis of 50%–90%, and the poor responders had tumor necrosis of 0%–50%, even though spontaneous necrosis in osteogenic sarcomas can reach 40%. It was assumed and supported by uni- and multivariate statistical analysis (Table II) that significant deviation exists between the survival of good responders and the rest of the osteogenic sarcoma patients ($P = 0.043$). It was surprising in our material, however, that the survival curve of the patients showing moderate response exhibited a course rather similar to that of the well-responding group compared with the poor responders. The latter group demonstrated a 5-year survival of only 40%.

The surgical stage of the tumor is of decisive prognostic significance. In around 10%–15% of osteogenic sarcoma cases, macroscopic pulmonary metastases are already observable at the time of recognition of the disease [9,35]. In that patient group, 5-year survival is around 10%–20% and was practically independent of the location of the primary tumor, preoperative chemotherapy, or the immediate surgical treatment. These findings are verified by our own results: of the 9 patients in group II, only 1 survived after 5 years with persisting pulmonary metastases; the rest had an average survival period of 20 months.

An important prognostic factor is the cooperation of the patient during chemotherapy or the patient's drug tolerance. Delayed, low-dose chemotherapy could possibly lead to the development of polyresistant tumor cell populations. Despite our third group's low case number (12 patients), a higher ratio of resistance to chemotherapy was evident. An explanation of this could be the older age of the patients (28.6 years vs. to 17.4 in group I). Patients >30 tend to have less tolerance toward intensive chemotherapy. Many authors [35,36,37] have called attention to the importance of initial intensive chemotherapy and the close relationship between methotrexate pharmacokinetics and prognosis in osteosarcoma. In our material, the survival curve of group III (Fig. 7) following inadequate chemotherapeutic treatment exhibited a poor survival curve similar to that of the patient group with metastatic osteogenic sarcoma. The noted 5-year survival rate for both groups corresponds to the 5-year survival of 10%–20% shown in documented control groups in which no chemotherapy was given [38].

CONCLUSIONS

It could be said that a favorable 5-year EFS rate of 65%–75% can only be achieved by means of appropriately wide or radical surgical margins and intensive chemotherapy given according to protocol. Without these, local recurrences and pulmonary metastases decrease the level of survival to the level of metastatic osteogenic sarcomas. In itself, age >30 is not a bad prognostic factor, but in this age group, poor cooperation and weak tolerance to chemotherapy are to be reckoned with, worsening the chances of survival. Apart from age, in our survey the duration of symptoms, radiographic appearance of the tumor, and patient's sex did not prove to be significant prognostic factors, even in univariate statistical analysis. Positive prognostic factors were tumor volume ≤ 60 cm^3,

wide or radical surgical margins, far distal location, <20% cartilage content of the tumor, and >90% tumor necrosis following preoperative chemotherapy. These latter 4 factors also proved to be significant variables for EFS during the course of multivariate analysis. To clarify the various conflicting questions, there is a need for their evaluation in randomized, prospective, uniformly treated, statistically adequate patient material.

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